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A mild and practical method for the regioselective synthesis of N-acylated 3,4-dihydropyrimidin-2-ones. New acyl transfer reagents

Kamaljit Singh* and Sukhdeep Singh

Organic Synthesis Laboratory, Department of Applied Chemical Sciences and Technology, Guru Nanak Dev University, Amritsar 143 005, India

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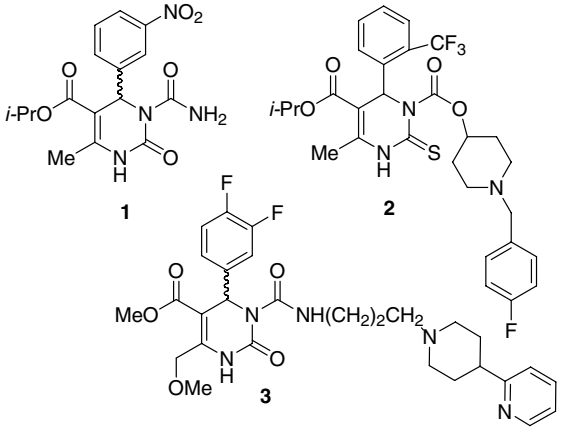
Abstract—The treatment of 3,4-dihydropyrimidin-2-ones with *n*-BuLi at −78 °C, followed by quenching with various electrophiles furnished *N*3-substituted derivatives, regioselectively. Further, *N*1,*N*3-diacyl derivatives were found to transfer *N*1-acyl groups to nucleophilic sites.

4-Aryl-3,4-dihydropyrimidin-2-ones (Biginelli compounds, DHPMs) represent an azaheterocyclic system of remarkable pharmacological profile.[1] DHPMs are found in natural products and find applications as calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, and hepatitis B virus replication suppressors. Several marine derived natural products which are inhibitors of HIV gp-120CD4, also contain the DHPM core. Although a large number of DHPM derivatives have been prepared in single-pot Biginelli multi-component reaction (MCR), and its variants, a greater number of very interesting heterocycles have been obtained by the chemical functionalization of the six (*N*1, C2, *N*3, C4, C5 and C6) positions around the DHPM core.[2]

Recently, we revealed that Biginelli DHPMs can be lithiated at the C6 methyl and thus elaborated regioselectively, with a wide variety of electrophiles.[3] Regioselective *N*3-functionalization (acylation, alkoxycarbonylation, and alkylation) of DHPMs is of considerable importance for the preparation of *N*3-substituted DHPMs, related to the biologically important compounds SQ 32,926 **1**, SQ 32,547 **2**, and L-771,668 **3**.[1a]



A survey of the literature revealed a single example of the direct *N*3-acylation ($DMF/POCl_3$) of a C-4 aryl-substituted DHPM, where the *N*3-formylated product (12% yield) was attended by a 6*H*-1,3-thiazine derivative (47% yield).[4] A rather high temperature (100–180 °C) microwave-aided acylation technique, employing polymer-supported reagents and scavengers provided an attractive method,[5] but lacked the economy and simplicity of a one-pot reaction. In contrast to the acylation, the alkoxycarbonylation of Biginelli DHPMs with, for example, ethyl chloroformate and base has proved problematic leading to mixtures of *N*1 and *N*3 substituted products depending on the substitution pattern around the DHPM ring.[6] Also, *N*3-monoalkylated DHPMs

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* Corresponding author. Tel.: +91 0183 2258853/2258802–09x3508; fax: +91 0183 2258819–20; e-mail: kamaljit19in@yahoo.co.in

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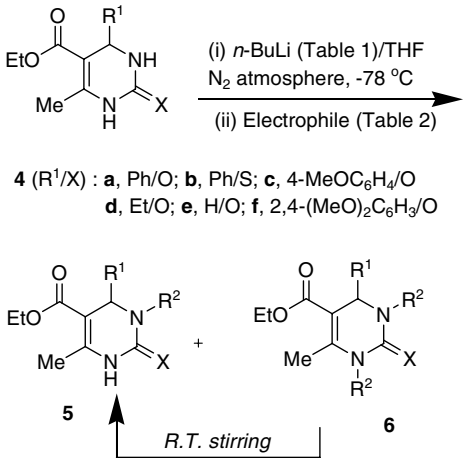


Scheme 1. Synthesis of *N*3-acylated DHPMs.

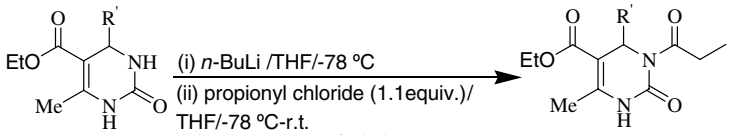
cannot be obtained by the alkylation of unsubstituted derivatives and when monoalkyl ureas are employed, only *N*1-alkylated DHPMs are formed.[7] Thus, a flexible, general, one-pot approach to drug-like DHPM derivatives, avoiding intricate isolation/purification techniques, is required.

In this letter, we report a one-pot and a highly efficient method that permits the rapid synthesis of *N*3-acylated DHPMs **5** which does not rely on the use of any sophisticated technique, but instead allows the use of a number of acylating agents. Our procedure involves a low temperature (−78 °C) lithiation of DHPMs **4** at *N*3, using *n*-BuLi and subsequent quenching with an acylating agent (Scheme 1).

During optimization experiments (Table 1), we noted that when the quantity of the base was greater than 1.1 equiv, the proportion of *N*3-acetylated DHPMs **5** decreased and, in some cases, C6,*N*3-diacyl derivatives were produced.[8] Also, under the optimized reaction conditions, employing a 1.1 equiv of the base, any *N*1,*N*3-diacyl derivative **6** formed, was converted into **5** (TLC) upon warming the reaction to room temperature. This finding suggested to us that the diacyl DHPM derivatives could be used as acyl transfer reagents.

3,4-Dihydropyrimidin-2-ones **4** were prepared according to the previously described procedures.[9] To generate the lithio anions, a suspension of **4** in dry THF, was treated with freshly prepared *n*-BuLi (2.0 N in hexanes, 1.1 equiv) at −78 °C under an atmosphere of dry nitrogen, and then the mixture was warmed to room temperature for 0.5 h before cooling back to −78 °C. The pale yellow colored[10] anions were then quenched by dropwise addition of the electrophiles (Table 2) in anhydrous THF at −78 °C. The reaction was allowed to warm to room temperature and stirred until complete (20–30 min, TLC) and then quenched with a cooled saturated solution of ammonium chloride. Some reactions (Table 2, entries 1–5 and 8–10), yielded solid products after the extractive work-up, which upon re-crystallization from DCM/hexane (1:1 v/v), furnished the corresponding pure product **5**; for the remaining reactions, chromatographic purification was required. When the reaction mixtures were treated with saturated ammonium chloride solution at −78 °C, in addition to product **5**, the *N*1,*N*3-diacyl derivatives **6** (Table 2) were also isolated. However, when the quenching was performed at room temperature, **5** was exclusively isolated, except entries 4, 12 and 17, where corresponding **6** accompanied the *N*3-acyl products, albeit in trace amounts (<5%). In order to improve the yield of **6**, an alternative method employing 2.5 equiv of potassium *tert*-butoxide in combination with 18-crown-6 was developed. All products were characterized by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. In order to eliminate the possibility that the diacyl compounds were *N*,*O*-diacyl derivatives, the structure of **6b** was additionally confirmed by X-ray crystal structure analysis (Fig. 1).[11] We believe that the regioselectivity arises from the relatively more reactive and higher proportion of the *N*3 anionic species, formed in situ, may produce the products of exclusive function-

Table 1. Optimization of the reaction conditions for *N*3-acylation of 3,4-dihydropyrimidin-2-ones



Entry	Equivalents of *n*-BuLi	Product	Isolated yield (%)
1	1.1	**5b**	90
2	1.1	**5j**	86
3	2.2	**5b**	52
4	2.2	**5j**	20
5	3.1	**5b**	43
6	3.1	**5j**	0[a] (<5%)
7	4.1	**5b**	30
8	4.1	**5j**	0[a] (<5%)

[a] The corresponding *N*3,C6-diacyl derivative was obtained. Values in parentheses represent the isolated yield of *N*3,C6-diacyl derivatives.

Table 2. Scope of the regioselective *N*3-acylation of 3,4-dihydropyrimidin-2-ones

Entry	4	Electrophile	Product				Isolated yields (%) 5	Mp (°C) 5
			5[a]/6[b]	R^1	R^2	X		
1	**4a**	MeCOCl	**5a**	Ph	COMe	O	92	170
2	**4a**	EtCOCl	**5b**	Ph	COEt	O	90[c]	202
3	**4a**	*n*-PrCOCl	**5c**	Ph	COPr-*n*	O	89	137
4	**4a**	PhCOCl	**5d**	Ph	COPh	O	91	151
5	**4a**	*p*-$NO_2C_6H_4COCl$	**5e**[d]	Ph	COC_6H_4–*p*NO_2	O	61	141
6	**4a**	*p*-$MeC_6H_4SO_2Cl$	**5f**[d]	Ph	$SO_2C_6H_4$–*p*Me	O	55	183
7	**4a**	α-$C_{10}H_7COCl$	**5g**[d]	Ph	CO-α$C_{10}H_7$	O	71	140
8	**4b**	EtCOCl	**5h**[e]	Ph	COEt	S	89	138
9	**4c**	EtCOCl	**5i**	4-$MeOC_6H_4$	COEt	O	91	157
10	**4d**	EtCOCl	**5j**	Et	COEt	O	86	134
11	**4e**	EtCOCl	**5k**[d]	H	COEt	O	75	143
12	**4f**	EtCOCl	**5l**	2,4-$(MeO)_2C_6H_3$	COEt	O	62	191
13	**4a**	$ClCH_2COCl$	**5m**[d]	Ph	$COCH_2Cl$	O	30	209
14	**4a**	ClCOCOOEt	**5n**[d]	Ph	$COCO_2Et$	O	69	104
15	**4a**	$BrCH_2CH_2COCl$	**5o**[d]	Ph	$COCH{=}CH_2$	O	30	179
16	**4a**	HCOOEt	**5p**[d]	Ph	CHO	O	65	222
17	**4a**	$BrCH_2COOEt$	**5q**	Ph	CH_2COOEt[f]	O	59	140
18	**4a**	MeCHBrCOOEt	**5r**[d]	Ph	MeCHCOOEt[f,g]	O	62	123

[a] *Method A*: (i) DHPM (1.0 equiv), *n*-BuLi (1.1 equiv)/−78 °C; (ii) E^+ (1.1 equiv)/−78 °C to rt; (iii) aqueous NH_4Cl (rt).
[b] Compounds **6a** (10%), **6b** (18%), **6c** (15%), **6d** (22%), **6i** (20%), **6j** (17%), **6l** (23%) and **6q** (7%) were formed employing *Method B*: [(i) DHPM (1.0 equiv), *n*-BuLi (1.1 equiv)/−78 °C; (ii) E^+ (1.1 equiv)/−78 °C (iii) aqueous NH_4Cl (−78 °C)] and **6b** (45%) using *Method C*: [(i) DHPM (20 mmol), $KBuO^t$ (87.5 mmol)/18-C-6 (7.5 mmol)/rt; (ii) E^+ (90 mmol)/0 °C to rt (24 h)].
[c] Formed in 85% yield when propionic anhydride was used as the electrophile.
[d] Corresponding **6** not formed.
[e] Corresponding **6h** was rapidly converted (TLC) into **5h** during work-up.
[f] *N*3-alkylated products were formed.
[g] A mixture of diastereomers (6:4) was obtained. For details, see Supplementary data.

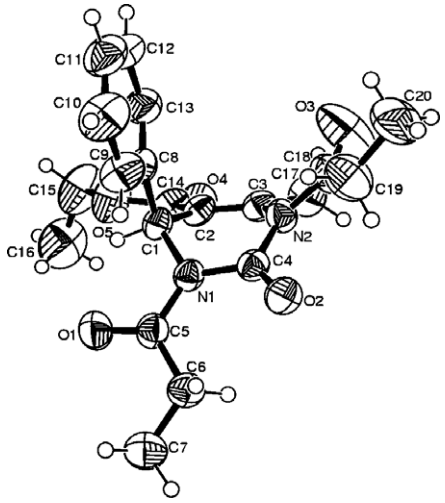
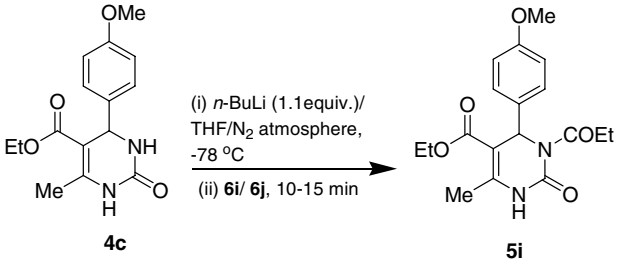


Figure 1. X-ray crystal structure of **6b** showing the stereoview of the molecule and the numbering scheme used in the structure analysis.

alization at *N*3. A particularly attractive feature of this method is its applicability to various electrophiles (Table 2), a feature lacking in the previous methods.[4,5] Further, the substitution pattern around the DHPM core was not found to influence the yield of **5**.

Acyl transfer to nucleophiles is an important transformation in organic synthesis. Several enzymes, such as serine acetyl transferase[12] are involved in the direct transfer of the acyl groups between reactants in biosynthesis in bacteria and plants.



Scheme 2. Acyl transfer from *N*1,*N*3-diacyl DHPMs.

The selective monoacylation of amino groups in the presence of other functional groups has significant utility[13] and several reagents have been developed for this purpose. We envisioned that **6** could be used to effect acyl transfers to various nucleophiles. As an example, when **4c** was treated with 1.1 equiv of *n*-BuLi and quenched with 1.0 equiv of *N*1,*N*3-disubstituted DHPM **6i/6j**, *N*3-substituted DHPM **5i** was obtained, exclusively, in 96–98% isolated yield (Scheme 2). These reactions demonstrate the potential of *N*1,*N*3-diacyl DHPM derivatives as acyl transfer reagents. Further investigations in determining scope and limitation of this reaction of DHPMs is under investigation.

Thus, in summary, we have developed a mild and general one-pot protocol for *N*3-acylation of Biginelli DHPMs, which tolerates various substituents around the DHPM nucleus. A facile acyl transfer from *N*1,*N*3-disubstituted DHPMs to give an *N*3-substituted DHPM has also been demonstrated.

Acknowledgements

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Supplementary data

Experimental procedures and spectral data for all compounds are given in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.039.

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8. In the case of entries 3, 9 and 10 (Table 2), when 3–4 equiv of *n*-BuLi was used, the corresponding N3,C6-diacylated products were obtained in low yields. However, entry 2 (Table 2) did not yield the corresponding *N*3,C6-diacylated product, and only *N*3-acylated product was isolated in 30% yield.
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10. In our previous investigation,[3] on deprotonation of the C6 Me of DHPMs, the trianion generated using LDA was of a blood red color.
11. Crystallographic data for **6b** have been deposited with the Cambridge Crystallographic Data Centre (CCDC). The coordinates can be obtained on request from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. The CCDC Number is 614958.
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